



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB97/01521 (22) International Filing Date: 6 June 1997 (06.06.97) (30) Priority Data: 9611947.4 7 June 1996 (07.06.96) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): COMINACINI, Luciano [IT/IT]; Istituto di Semeiotica e Nefrologia Medica, Ospedale Policlinico, I-37134 Verona (IT). (74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MEDICAMENTS FOR AMELIORATING ENDOTHELIAL CELL ACTIVATION <div style="text-align: center;"> <p>Chemical structure (I) is a substituted benzene ring with substituents R⁴, R⁵, R⁶, and R³O. The ring is connected via an oxygen atom to a chain containing a thiazolidine ring and a carbonyl group. The chain is represented as: (CH₂)_n - O - C₆H₄ - CH₂ - CH - C(=Y) - NH - Z, where the thiazolidine ring is fused to the CH₂ group.</p> </div> (57) Abstract <p>The use of a compound of formula (I) in which: R¹ and R² are the same or different and each represents a hydrogen atom or a C₁ - C₅ alkyl group; R³ represents a hydrogen atom, a C₁ - C₆ aliphatic acyl group, a (C₅ - C₇ cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a (C₁ - C₆ alkoxy) carbonyl group or a benzoyloxycarbonyl group; R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₁ - C₅ alkyl group or a C₁ - C₅ alkoxy group, or R⁴ and R⁵ together represent a C₁ - C₄ alkylenedioxy group; n is 1, 2 or 3; W represents the -CH₂, > CO or > CH-OR⁶ group (in which R⁶ represents any one of the atoms or groups defined for R³ and may be the same as or different from R³); and Y and Z are the same or different and each represents an oxygen atom or an imino (-NH) group; or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the amelioration of inappropriate endothelial cell activation.</p>		

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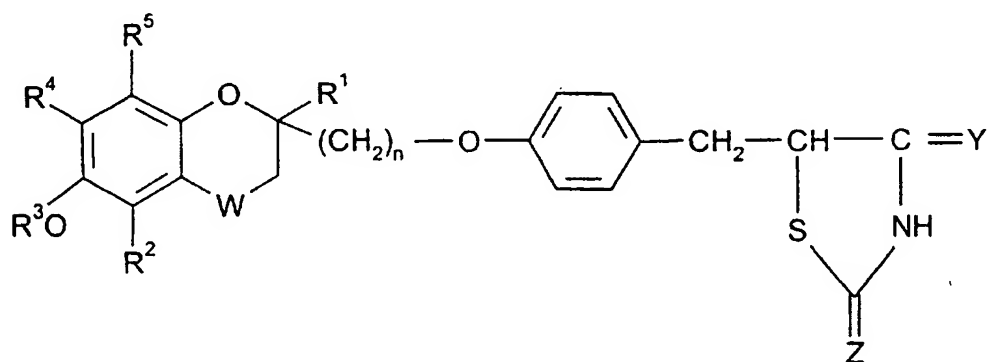
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MEDICAMENTS FOR AMELIORATING ENDOTHELIAL CELL ACTIVATION

The present invention relates to the use of thiazolidine derivatives for ameliorating endothelial cell activation.

European patent no. 0139421 describes thiazolidine derivatives of formula (I):



in which:

R^1 and R^2 are the same or different and each represents a hydrogen atom or a $C_1 - C_5$ alkyl group;

R^3 represents a hydrogen atom, a $C_1 - C_6$ aliphatic acyl group, a ($C_5 - C_7$ cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a ($C_1 - C_6$ alkoxy) carbonyl group or a benzoyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a $C_1 - C_5$ alkyl group or a $C_1 - C_5$ alkoxy group, or R^4 and R^5 together represent a $C_1 - C_4$ alkylendioxy group;

n is 1, 2 or 3;

W represents the -CH-, >CO or >CH-OR⁶ group (in which R⁶ represents any one of the atoms or groups defined for R³ and may be the same as or different from R³); and

5

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

and pharmaceutically acceptable salts thereof.

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The compounds are said to show blood lipid metabolism ameliorating activity and to have the ability to decrease the levels of blood lipid peroxides, blood triglycerides and blood cholesterol.

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International patent application publication no. WO94/19347 describes the ability of compounds of formula (I) to inhibit the oxidation and/or peroxidation of low density lipoprotein (LDL) and suggests that the compounds may therefore have utility in the treatment of arteriosclerosis.

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We have now surprisingly found that compounds of formula (I) reduce the activation of endothelial cells and are therefore useful in the treatment of disorders associated with endothelial cell activation.

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The vascular endothelium maintains a non-thrombogenic surface on the inside of blood vessels, regulates the growth and differentiation of underlying tissues and plays a pivotal role in controlling trafficking of leukocytes in inflammatory conditions. Perturbations in endothelial functioning are implicated in many diseases, including atherosclerotic and inflammatory diseases.

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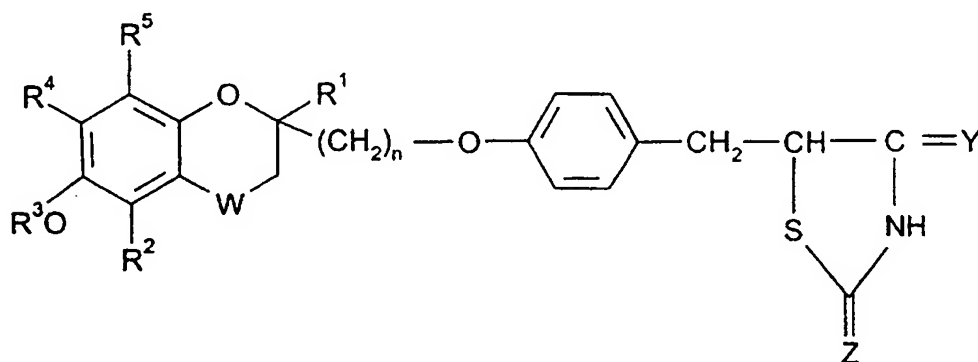
Activation of the endothelial cell in post-capillary venules leads to increased expression of adhesion molecules and consequent recruitment of blood leukocytes into adventitial tissue. Whilst this is a necessary step in the physiological defence mechanisms to foreign bodies, inappropriate endothelial cell activation is implicated in pathological inflammatory states.

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The activation state of endothelial cells is at least in part determined by the effect of so-called inflammatory mediators, such as $\text{TNF}\alpha$, interleukin-1. These agents are secreted by inflammatory cells, and cause activation of endothelial cells. A typical response of endothelial cells to such activation is to increase expression of adhesion molecules on the cell surface which allows recruitment of blood leukocytes to sites of inflammation. Therefore the level of adhesion molecules on the surface of endothelial cells can be taken as a measure of activation of the cells under inflammatory stimulus.

Such endothelial cell activation is also thought to be the initiating event for atherosclerotic cardiovascular disease. These arterial plaques contain macrophages and lymphocytes recruited from plasma by adhesion molecules on the endothelial cell surface. The macrophages in particular have been implicated in the acute symptoms (such as angina pectoris, myocardial infarction) associated with atherosclerotic plaques.

In a first aspect, the present invention provides the use of a compound of formula (I):



in which:

R^1 and R^2 are the same or different and each represents a hydrogen atom or a $C_1 - C_5$ alkyl group;

R^3 represents a hydrogen atom, a $C_1 - C_6$ aliphatic acyl group, a ($C_5 - C_7$ cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or

naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a (C₁ - C₆ alkoxy) carbonyl group or a benzoyloxycarbonyl group;

R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₁ - C₅ alkyl group or a C₁ - C₅ alkoxy group, or R⁴ and R⁵ together represent a C₁ - C₄ alkylenedioxy group;

n is 1, 2 or 3;

W represents the -CH₂, >CO or >CH-OR⁶ group (in which R⁶ represents any one of the atoms or groups defined for R³ and may be the same as or different from R³); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the amelioration of inappropriate endothelial cell activation.

In a second or alternative aspect, the invention provides a method for the treatment of an animal, including man, suffering from inappropriate endothelial cell activation, which method comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

As will be appreciated by those skilled in the art, references herein to treatment extend to prophylaxis as well as to the treatment of established disorders or symptoms thereof.

In a preferred aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a

a medicament for the amelioration of endothelial cell activation in atherosclerotic cardiovascular disease, including angina, myocardial infarction, peripheral vascular disease and cerebrovascular disease.

- 5 The invention further provides a method for the amelioration of endothelial cell activation in an animal, including man, suffering from atherosclerotic cardiovascular disease, including angina, myocardial infarction, peripheral vascular disease and cerebrovascular disease which method comprises administration of an effective amount of a compound of formula (I) or a
10 pharmaceutically acceptable salt thereof.

In a further preferred aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of an inflammatory disorder
15 associated with inappropriate endothelial cell activation.

The invention further provides a method for the treatment of an animal, including man, suffering from an inflammatory disorder associated with inappropriate endothelial cell activation, which method comprises administration
20 of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Inflammatory disorders associated with inappropriate endothelial cell activation include, for example, rheumatoid arthritis; systemic lupus erythematosus; renal diseases including glomerulonephritis; hypertension and complications thereof;
25 tissue reperfusion damage; adult respiratory distress syndrome; radiation-induced injuries; burns; inflammation in asthma, influenza and chronic bronchitis; inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease, non-steroidal anti-inflammatory drug induced damage and inflammatory and secretory effects of
30 bacterial infection, e.g. due to *Clostridium difficile*; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge (i.e. urinary) incontinence; eye and dental inflammation, e.g.

gingivitis and periodontitis; and neurodegenerative diseases such as Alzheimer's disease.

5 It will be appreciated by those skilled in the art that formula (I) is intended to include all stereoisomers, including enantiomers and diastereoisomers, and mixtures thereof including racemates.

In compounds of formula (I) it is preferred that:

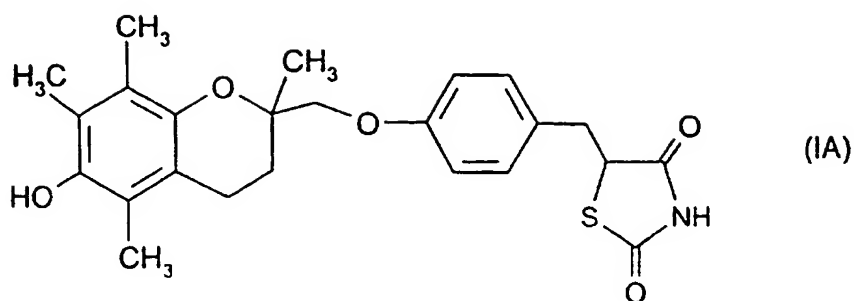
- 10 R^1 represents C_{1-4} alkyl;
 R^2 represents H or C_{1-3} alkyl;
 R^3 represents H, C_{1-4} aliphatic acyl, unsubstituted C_{7-11} aromatic acyl or C_{2-4} alkoxycarbonyl;
 R^4 represents C_{1-4} alkyl; and
15 R^5 represents H or C_{1-3} alkyl.
More preferably R^3 represents H, acetyl, benzoyl or ethoxycarbonyl.

Most preferably:

- 20 R^1 represents methyl;
 R^2 represents H or methyl;
 R^3 represents H, acetyl or ethoxycarbonyl;
 R^4 represents methyl or t-butyl; and
 R^5 represents H or methyl.

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A particularly preferred compound for use in accordance with the present invention is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, represented by formula (IA):



The compound of formula (IA) is also known as troglitazone.

- 5 Compounds of formula (I) and their pharmaceutically acceptable salts may be prepared as described in EP 0139421.

It will be appreciated that the amount of a compound of formula (I) required for use in treatment according to the invention will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.5 to about 20mg/kg of bodyweight per day preferably in the range of 0.1 to 15 mg/kg/day, most preferably in the range of 1 to 10mg/kg/day, such as about 50 - 500mg per day for a normal adult.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 800mg, conveniently 20 to 500mg, most conveniently 50 to 500mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

- 5 A pharmaceutical formulation will comprise a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.
- 10

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. Oral and parenteral administration are preferred. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

15

20

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a pre-determined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary, or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents. The tablets may be coated

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according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain
5 conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or
10 continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and /or dispersing agents. Alternatively, the
15 active ingredient may be in powder form, obtained by a aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the combinations according to the
20 invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents,
25 dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as

gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

5 Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other commonly used, materials in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

10

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, paste, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be carriers.

15 For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

20 Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurised packs.

25 For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebuliser or a pressure pack or other convenient means of delivering an aerosol spray. Pressurised packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a value to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical compositions for use in the present invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The inhibitory effect of the compound of formula (IA) on endothelial cell activation is demonstrated by the following Examples, which are illustrative of the present invention and not limitative thereof.

The invention is further illustrated by the following non-limitative example.

Example:

Endothelial cells from human umbilical veins (HUVECs) were isolated by conventional methods, maintained in culture and used between passages 2 and 4.

To aid solubility of troglitazone, human low density lipoprotein (isolated by serial density centrifugation) was used as a carrier. 5µg of troglitazone was incubated with LDL for 24h at 4°C in M-199 medium containing 10% foetal calf serum. Troglitazone containing LDL was purified by gel-filtration and any contaminating endotoxin removed by passing the troglitazone over a pre-packed endotoxin affinity column.

Troglitazone-containing LDL was incubated with HUVECs in M-199 medium at 37°C for 24h. After this time the troglitazone-containing medium was removed.

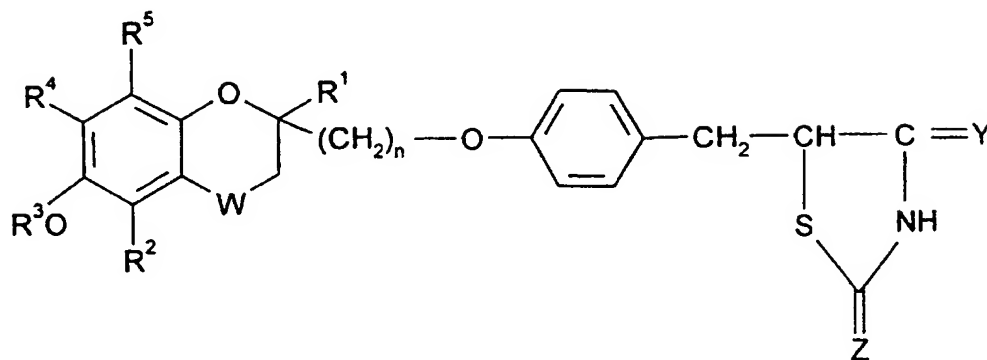
5 The HUVECs were incubated with $\text{TNF}\alpha$ (100U/ml, Sigma) in M-199 medium at 37°C for 24h. After this time, the level of VCAM-1 on the cell surface was measured using antibody detection in a FACS machine by conventional methods.

10 The results are presented in Figure 1.

The presence of troglitazone in the pre-incubation clearly attenuates the expression of the adhesion molecule VCAM-1 in response to the inflammatory mediator $\text{TNF}\alpha$.

Claims

1. The use of a compound of formula (I):



5 in which:

- R^1 and R^2 are the same or different and each represents a hydrogen atom or a $C_1 - C_5$ alkyl group;
- 10 R^3 represents a hydrogen atom, a $C_1 - C_6$ aliphatic acyl group, a ($C_5 - C_7$ cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more
- 15 oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a ($C_1 - C_6$ alkoxy) carbonyl group or a benzoyloxycarbonyl group;
- R^4 and R^5 are the same or different and each represents a hydrogen atom, a $C_1 - C_5$
- 20 alkyl group or a $C_1 - C_5$ alkoxy group, or R^4 and R^5 together represent a $C_1 - C_4$ alkylenedioxy group;
- n is 1, 2 or 3;
- 25 W represents the $-CH_2$, $>CO$ or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

5 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the amelioration of inappropriate endothelial cell activation.

2. Use of a compound according to Claim 1 wherein;

R¹ represents C₁₋₄ alkyl;

R² represents H or C₁₋₃ alkyl;

10 R³ represents H, C₁₋₄ aliphatic acyl, unsubstituted C₇₋₁₁ aromatic acyl or C₂₋₄ alkoxycarbonyl;

R⁴ represents C₁₋₄ alkyl

and

R⁵ represents C₁₋₃ alkyl

15 or a pharmaceutically acceptable salt thereof.

3. Use of a compound according to Claim 2 wherein R³ represents H, acetyl, benzoyl or ethoxycarbonyl, or a pharmaceutically acceptable salt thereof.

20 4. Use of a compound according to claim 2 wherein;

R¹ represents methyl;

R² represents H or methyl;

R³ represents H, acetyl or ethoxycarbonyl

R⁴ represents methyl or t-butyl and

25 R⁵ represents H or methyl,

or a pharmaceutically acceptable salt thereof.

5. Use according to claim 1 where the compound is troglitazone.

30 6. A method for the treatment of an animal, including man, suffering from inappropriate endothelial cell activation which method comprises administration or a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

7. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the amelioration of endothelial cell activation in atherosclerotic cardiovascular disease.
- 5 8. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of an inflammatory disorder associated with inappropriate endothelial cell activation.

EFFECT OF TROGLITAZONE ON TNF-INDUCED
VCAM EXPRESSION ON HUVECS

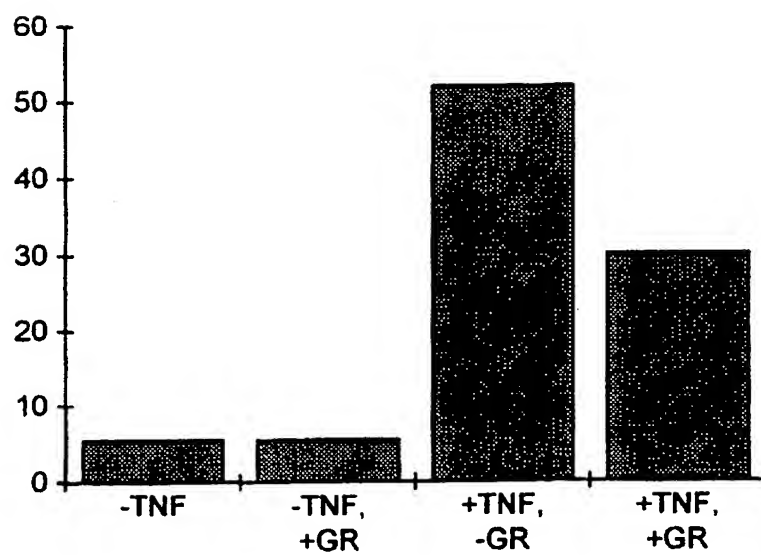


FIG. 1

INTERNATIONAL SEARCH REPORT

national Application No

PCT/GB 97/01521

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LAW: "Troglitazone inhibits vascular smooth muscle cell growth and intimal hyperplasia" J. CLIN. INVEST., vol. 98, no. 8, 15 October 1996, pages 1897-1905, XP002042268 see the whole document	1-6
A	EP 0 139 421 A (SANKYO COMPANY LTD) 2 May 1985 cited in the application see whole document, especially pages 119-121	1-7
A	WO 94 19347 A (SANKYO COMPANY LTD) 1 September 1994 cited in the application see abstract	1-7
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Information on patent family members

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Information on patent family members

National Application No

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International Application No
PCT/GB 97/01521

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 6
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.